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(54) Title: SUBSTITUTED INDOLYLPROPYL-PIPERAZINE DERIVATIVES AS 5-$HT_{1DALPHA}$ AGONISTS

(57) Abstract

A class of 1-[3-(1*H*-indol-3-yl)propyl]-4-(2-phenylethyl)piperazine derivatives, substituted at the 5-position of the indole nucleus by a five-membered heteroaromatic moiety, on one or other of the ethylene carbon atoms of the phenethyl moiety by halogen, trifluoromethyl, alkyl, hydroxyalkyl or alkoxyalkyl, and optionally on the phenyl ring of the phenethyl moiety by halogen, trifluoromethyl, alkoxy or an oxazolidinone group and optionally by one or two further substituents, are selective agonists of 5-HT_1-like receptors, being potent agonists of the human 5-$HT_{1D\alpha}$ receptor subtype whilst possessing at least a 10-fold selective affinity for the 5-$HT_{1D\alpha}$ receptor subtype relative to the 5-$HT_{1D\beta}$ subtype; they are therefore useful in the treatment and/or prevention of clinical conditions, in particular migraine and associated disorders, for which a subtype-selective agonist of 5-HT_{1D} receptors is indicated, whilst eliciting fewer side-effects, notably adverse cardiovascular events, than those associated with non-subtype-selective 5-HT_{1D} receptor agonists.

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SUBSTITUTED INDOLYLPROPYL-PIPERAZINE DERIVATIVES AS 5-HT1DALPHA AGONISTS

The present invention relates to a class of substituted piperazine derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT_1-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

It has been known for some time that 5-HT_1-like receptor agonists which exhibit selective vasoconstrictor activity are of use in the treatment of migraine (see, for example, A. Doenicke *et al., The Lancet*, 1988, Vol. 1, 1309-11; and W. Feniuk and P.P.A. Humphrey, *Drug Development Research*, 1992, **26**, 235-240).

The human 5-HT_1-like or 5-HT_{1D} receptor has recently been shown by molecular cloning techniques to exist in two distinct subtypes. These subtypes have been termed 5-HT_{1D_α} (or $5\text{-HT}_{1D\text{-}1}$) and 5-HT_{1D_β} (or $5\text{-HT}_{1D\text{-}2}$), and their amino acid sequences are disclosed and claimed in WO-A-91/17174.

The 5-HT_{1D_α} receptor subtype in humans is believed to reside on sensory terminals in the dura mater. Stimulation of the 5-HT_{1D_α} subtype inhibits the release of inflammatory neuropeptides which are thought to contribute to the headache pain of migraine. The human 5-HT_{1D_β} receptor subtype, meanwhile, is located predominantly on the blood vessels and in the brain, and hence may play a part in mediating constriction of cerebral and coronary arteries, as well as CNS effects.

Administration of the prototypical 5-HT_{1D} agonist sumatriptan (GR43175) to humans is known to give rise at therapeutic doses to certain adverse cardiovascular events (see, for example, F. Willett *et al., Br. Med. J.*, 1992, **304**, 1415; J.P. Ottervanger *et al., The Lancet*, 1993, **341**, 861-2; and D.N. Bateman, *The Lancet*, 1993, **341**, 221-4). Since sumatriptan barely discriminates between the human 5-HT_{1D_α} and 5-HT_{1D_β} receptor subtypes (cf. WO-A-91/17174, Table 1), and since it is the blood vessels

with which the 5-HT$_{1D_\beta}$ subtype is most closely associated, it is believed that the cardiovascular side-effects observed with sumatriptan can be attributed to stimulation of the 5-HT$_{1D_\beta}$ receptor subtype. It is accordingly considered (cf. G.W. Rebeck *et al., Proc. Natl. Acad. Sci. USA*, 1994, **91**, 3666-9) that compounds which can interact selectively with the 5-HT$_{1D_\alpha}$ receptor subtype, whilst having a less pronounced action at the 5-HT$_{1D_\beta}$ subtype, might be free from, or at any rate less prone to, the undesirable cardiovascular and other side-effects associated with non-subtype-selective 5-HT$_{1D}$ receptor agonists, whilst at the same time maintaining a beneficial level of anti-migraine activity.

The compounds of the present invention, being selective 5-HT$_1$-like receptor agonists, are accordingly of benefit in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine. In particular, the compounds according to this invention are potent agonists of the human 5-HT$_{1D_\alpha}$ receptor subtype. Moreover, the compounds in accordance with this invention have been found to possess at least a 10-fold selective affinity for the 5-HT$_{1D_\alpha}$ receptor subtype relative to the 5-HT$_{1D_\beta}$ subtype, and they can therefore be expected to manifest fewer side-effects than those associated with non-subtype-selective 5-HT$_{1D}$ receptor agonists.

Several distinct classes of substituted five-membered heteroaromatic compounds are described in published European patent application 0497512, and published International patent applications 93/18029, 94/02477 and 94/03446. The compounds described therein are stated to be agonists of 5-HT$_1$-like receptors, and accordingly to be of particular use in the treatment of migraine and associated conditions. None of these publications, however, discloses nor even suggests the substituted piperazine derivatives provided by the present invention.

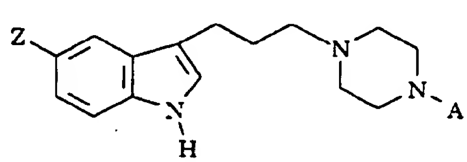
In EP-A-0548813 is described a series of alkoxypyridin-4-yl and alkoxypyrimidin-4-yl derivatives of indol-3-ylalkylpiperazines which are

alleged to provide treatment of vascular or vascular-related headaches, including migraine. There is, however, no disclosure nor any suggestion in EP-A-0548813 of replacing the alkoxypyridine or alkoxypyrimidine substituent with a substituted phenylethyl moiety; nor is there any suggestion therein that the range of substituents specified at the 5-position of the indole moiety might be replaced by an imidazole or triazole ring.

Moreover, nowhere in the prior art mentioned above is there any disclosure of a subtype-selective 5-HT_{1D} receptor agonist having a 5-HT_{1D_α} receptor binding affinity (IC_{50}) below 50 nM and at least a 10-fold selective affinity for the 5-HT_{1D_α} receptor subtype relative to the 5-HT_{1D_β} subtype.

The compounds according to the present invention are subtype-selective 5-HT_{1D} receptor agonists having a human 5-HT_{1D_α} receptor binding affinity (IC_{50}) below 50 nM, typically below 10 nM and preferably below 1 nM; and at least a 10-fold selective affinity, typically at least a 50-fold selective affinity and preferably at least a 100-fold selective affinity, for the human 5-HT_{1D_α} receptor subtype relative to the 5-HT_{1D_β} subtype. Moreover, the compounds in accordance with this invention possess interesting properties in terms of their efficacy and/or bioavailability.

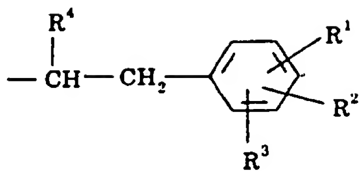
The present invention provides a compound of formula I, or a salt or prodrug thereof:



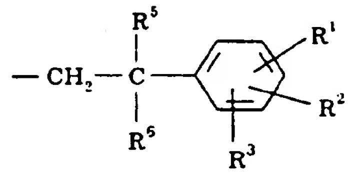
(I)

wherein

A represents a group of formula (i) or (ii):



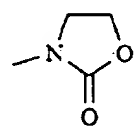
(i)



(ii)

in which

R^1 represents hydrogen, halogen, trifluoromethyl, C_{1-6} alkoxy or a group of formula (a):

 ;

(a)

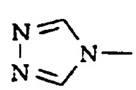
R^2 and R^3 independently represent hydrogen, halogen, trifluoromethyl or C_{1-6} alkoxy;

R^4 represents C_{1-6} alkyl, hydroxy(C_{1-6})alkyl or C_{1-6} alkoxy(C_{1-6})alkyl;

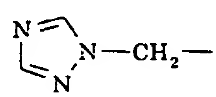
R^5 represents halogen, trifluoromethyl, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl or C_{1-6} alkoxy(C_{1-6})alkyl; and

R^6 represents hydrogen or halogen;

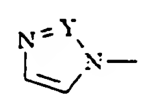
Z represents a group of formula (Za), (Zb) or (Zc):



(Za)



(Zb)



(Zc)

in which

Y represents nitrogen or C-R^7; and

R^7 represents hydrogen or C_{1-6} alkyl.

The present invention also provides compounds of formula I above, and salts and prodrugs thereof, wherein A represents a group of formula (i) or (ii) in which R^5 represents C_{1-6} alkyl, hydroxy(C_{1-6})alkyl or C_{1-6} alkoxy(C_{1-6})alkyl, and R^6 represents hydrogen; and Z represents a group of formula (Za) as defined above.

The compounds in accordance with the present invention are encompassed within the generic scope of co-pending International Patent Application No. PCT/GB95/01129, published as WO 95/32196 on 30 November 1995. There is, however, no specific disclosure therein of compounds corresponding to those of formula I above wherein A and Z are as defined above.

As used herein, the expression "C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl and *tert*-butyl. Derived expressions such as "C_{1-6} alkoxy" are to be construed accordingly.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine or chlorine, and particularly fluorine.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be

functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention have at least one asymmetric centre, and they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In the compounds of formula I above, the moiety R^1 suitably represents hydrogen, fluoro, trifluoromethyl, methoxy or a group of formula (a) as defined above. Particular values of R^1 include hydrogen and fluoro.

Suitably, R^2 and R^3 independently represent hydrogen, fluoro, trifluoromethyl or methoxy, in particular hydrogen or fluoro. Suitably, one or both of R^2 and R^3 represents hydrogen.

Particular values of R^4 include methyl, hydroxymethyl and methoxymethyl.

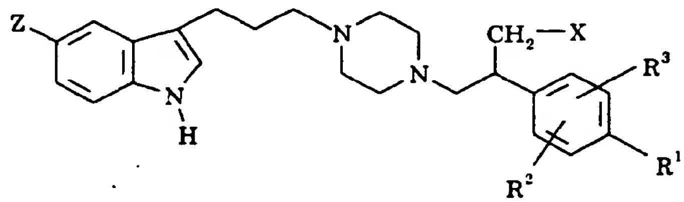
Particular values of R^5 include fluoro, trifluoromethyl, methyl, hydroxymethyl and methoxymethyl.

Suitably, R^6 represents hydrogen or fluoro, especially hydrogen.

Suitably, the variable Y in formula (Zc) represents nitrogen, CH or C-methyl.

Suitably, R^7 represents hydrogen or methyl, especially hydrogen.

A particular sub-class of compounds according to the invention is represented by the compounds of formula II, and salts and prodrugs thereof:



(II)

wherein Z, R^1, R^2 and R^3 are as defined above; and

X represents hydrogen, hydroxy or methoxy.

Particular values of R^1 in relation to formula II above include hydrogen and fluoro.

In one embodiment of the compounds of formula II above, R^2 is hydrogen and R^3 is other than hydrogen.

In another embodiment of the compounds of formula II above, R^2 and R^3 are both hydrogen.

In a typical aspect of the compounds of formula II above, Z represents a group of formula (Za) as defined above.

In another aspect of the compounds of formula II above, Z represents a group of formula (Zb) as defined above.

Suitably, X is hydrogen.

Specific compounds within the scope of the present invention include:

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(3-hydroxy-2-phenylpropyl)piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(3-methoxy-2-phenylpropyl)piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)-3-hydroxypropyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)prop-2-yl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-hydroxyprop-2-yl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-methoxyprop-2-yl]piperazine;

1-[3-(5-(imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-(2-phenylpropyl)piperazine;

1-[3-(5-(imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine;

1-[3-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(3-fluorophenyl)-3-methoxypropyl]piperazine;

1-[3-(5-(1,2,3-triazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(3-fluorophenyl)-3,3,3-trifluoropropyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(2,2-difluoro-2-phenylethyl)piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(3-fluorophenyl)-3-hydroxypropyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(2-phenylpropyl)-piperazine;

1-[3-(5-(2-methylimidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine;

and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for

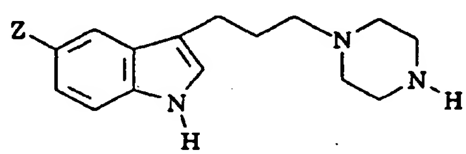
administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component. the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar

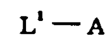
pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds according to the invention may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:



(III)



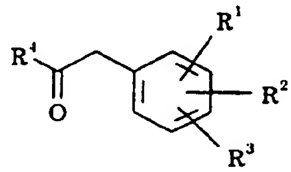
(IV)

wherein A and Z are as defined above, and L^1 represents a suitable leaving group.

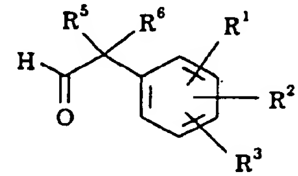
The leaving group L^1 is suitably a halogen atom, e.g. chlorine or bromine, or an alkylsulphonyloxy or arylsulphonyloxy group, e.g. methanesulphonyloxy (mesyloxy) or *p*-toluenesulphonyloxy (tosyloxy).

The reaction between compounds III and IV is conveniently effected by stirring the reactants under basic conditions in a suitable solvent, for example triethylamine in *N,N*-dimethylformamide or isopropanol, typically in the presence of sodium iodide.

In another procedure, the compounds according to the invention wherein A represents a group of formula (i) or (ii) as defined above may be prepared by a process which comprises reacting a compound of formula III as defined above with a compound of formula VA or VB respectively:



(VA)

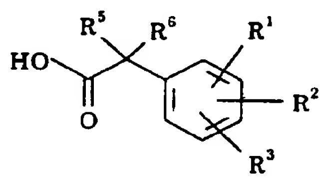


(VB)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above; in the presence of a reducing agent.

A suitable reducing agent for effecting this process is sodium cyanoborohydride, and the reaction is conveniently carried out in methanol or methanol/acetic acid at room temperature.

In a further procedure, the compounds according to the invention wherein A represents a group of formula (ii) as defined above may be prepared by a process which comprises reacting a compound of formula III as defined above with a carboxylic acid derivative of formula VI:

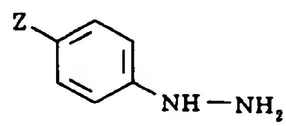


(VI)

wherein R^1, R^2, R^3, R^5 and R^6 are as defined above; in the presence of a condensing agent; followed by treatment with a reducing agent such as diisobutylaluminium hydride or borane-tetrahydrofuran.

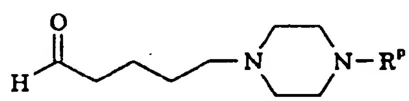
Condensing agents suitable for use in conjunction with the above process comprise 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenzotriazole hydrate, or bis(2-oxo-3-oxazolidinyl)phosphinic chloride in triethylamine.

The compounds of formula III above may be prepared by a process which comprises reacting a compound of formula VII:



(VII)

wherein Z is as defined above; with a compound of formula VIII, or a carbonyl-protected form thereof:



(VIII)

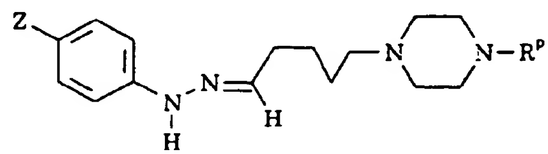
wherein R^p represents an amino-protecting group; with subsequent removal of the amino-protecting group R^p.

The reaction between compounds VII and VIII, which is an example of the well-known Fischer indole synthesis, is suitably carried out by heating the reagents together under mildly acidic conditions, e.g. 4% sulphuric acid at reflux.

Suitable carbonyl-protected forms of the compounds of formula VIII include the dimethyl acetal derivatives.

The protecting group R^p in the compounds of formula VIII is suitably a carbamoyl moiety such as *tert*-butoxycarbonyl (BOC), which can conveniently be removed as necessary by treatment under mildly acidic conditions. Indeed, the acidic conditions of the Fischer indole synthesis reaction will generally suffice to remove the BOC group.

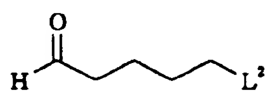
The Fischer reaction between compounds VII and VIII may be carried out in a single step, or may proceed via an initial non-cyclising step at a lower temperature to give an intermediate of formula IX:



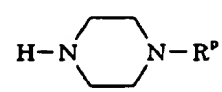
(IX)

wherein Z and R^p are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

The intermediates of formula VIII, or carbonyl-protected forms thereof, may be prepared by reacting a compound of formula X, or a carbonyl-protected form thereof, with a compound of formula XI:



(X)



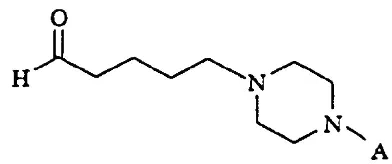
(XI)

wherein R^p is as defined above, and L^2 represents a suitable leaving group.

The leaving group L^2 is suitably a halogen atom, e.g. chlorine or bromine.

Where L^2 represents a halogen atom, the reaction between compounds X and XI is conveniently effected by stirring the reactants under basic conditions in a suitable solvent, for example sodium carbonate or potassium carbonate in 1,2-dimethoxyethane or *N,N*-dimethylformamide, or triethylamine in tetrahydrofuran or acetonitrile, optionally in the presence of sodium iodide.

The compounds according to the invention may alternatively be prepared by a process which comprises reacting the appropriate compound of formula VII as defined above with a compound of formula XII, or a carbonyl-protected form thereof:

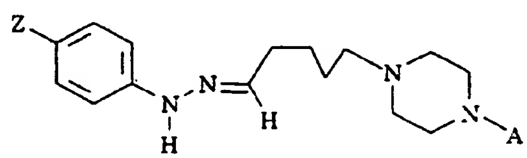


(XII)

wherein A is as defined above; under conditions analogous to those described above for the reaction between compounds VII and VIII.

As for the compounds of formula VIII, suitable carbonyl-protected forms of the compounds of formula XII include the dimethyl acetal derivatives.

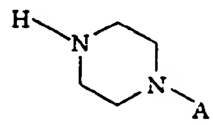
As with that between compounds VII and VIII, the Fischer reaction between compounds VII and XII may be carried out in a single step, or may proceed via an initial non-cyclising step at a lower temperature to give an intermediate of formula XIII:



(XIII)

wherein Z and A are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

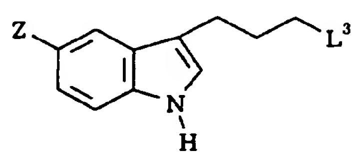
The intermediates of formula XII, or carbonyl-protected forms thereof, may be prepared by reacting a compound of formula X as defined above, or a carbonyl-protected form thereof, with a compound of formula XIV:



(XIV)

wherein A is as defined above; under conditions analogous to those described above for the reaction between compounds X and XI.

In an alternative procedure, the compounds of formula III above may be prepared by a process which comprises reacting a compound of formula XI as defined above with a compound of formula XV:



(XV)

wherein Z is as defined above, and L^3 represents a suitable leaving group; followed by removal of the amino-protecting group R^p.

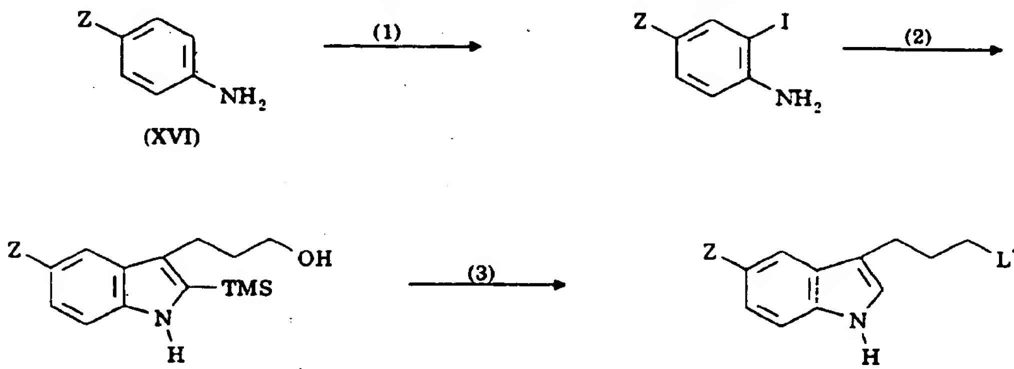
Similarly, the compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula XIV as defined above with a compound of formula XV as defined above.

The leaving group L^3 is suitably an alkylsulphonyloxy or arylsulphonyloxy group, e.g. methanesulphonyloxy (mesyloxy) or *p*-toluenesulphonyloxy (tosyloxy).

Where L^3 represents an alkylsulphonyloxy or arylsulphonyloxy group, the reaction between compound XV and compound XI or XIV is conveniently carried out in a suitable solvent such as 1,2-dimethoxyethane or isopropyl alcohol, typically in the presence of a base such as sodium

carbonate or potassium carbonate, optionally with the addition of sodium iodide.

In one representative approach, the compounds of formula XV wherein L^3 represents a mesyloxy or tosyloxy group may be prepared by the sequence of steps illustrated in the following reaction scheme (cf. Larock and Yum, *J. Am. Chem. Soc.*, 1991, **113**, 6689):



wherein Z is as defined above, L^4 represents mesyloxy or tosyloxy, and TMS is an abbreviation for trimethylsilyl.

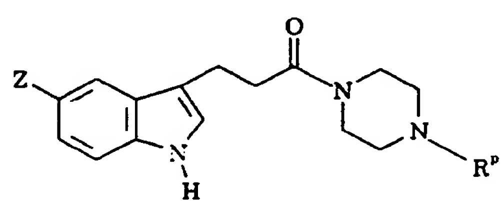
In Step 1 of the reaction scheme, the aniline derivative XVI is treated with iodine monochloride, advantageously in methanol in the presence of a base such as calcium carbonate, in order to introduce an iodine atom *ortho* to the amine moiety. Step 2 involves a palladium-mediated coupling reaction with the protected acetylene derivative TMS-C≡C-$(CH_2)_3$-OH, typically using palladium acetate and triphenylphosphine in the presence of lithium chloride and sodium carbonate, suitably in *N,N*-dimethylformamide at an elevated temperature. This is followed in Step 3 by removal of the TMS moiety, ideally in refluxing methanolic hydrochloric acid; followed in turn by mesylation or tosylation, suitably by using mesyl chloride or tosyl chloride respectively in pyridine.

In another representative approach, the compounds of formula XV wherein L^3 represents a mesyloxy or tosyloxy group may be prepared by

reacting 3,4-dihydro-2*H*-pyran with the appropriate compound of formula VII as defined above or a salt thereof, under a variant of the Fischer reaction conditions as described above for the reaction between compounds VII and VIII; followed by mesylation or tosylation of the 3-hydroxypropyl-indole derivative thereby obtained, typically by treatment with mesyl chloride or tosyl chloride under standard conditions.

The Fischer reaction with 3,4-dihydro-2*H*-pyran is suitably brought about by heating the appropriate hydrazine derivative VII or an acid addition salt thereof, typically the hydrochloride salt, in an inert solvent such as dioxan, advantageously in the presence of a mineral acid such as hydrochloric acid or a Lewis acid such as zinc chloride, at the reflux temperature of the solvent.

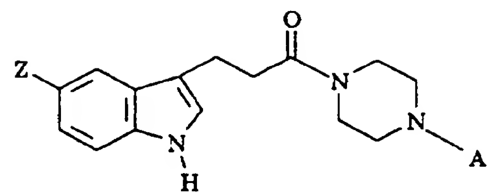
In a yet further procedure, the compounds of formula III above may be prepared by a process which comprises reducing a compound of formula XVII:



(XVII)

wherein Z and R^p are as defined above; with subsequent removal of the amino-protecting group R^p.

Similarly, the compounds according to the invention may be prepared by a process which comprises reducing a compound of formula XVIII:

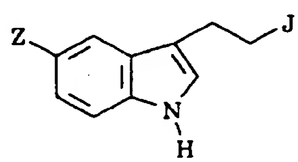


(XVIII)

wherein Z and A are as defined above.

The reduction of compound XVII or compound XVIII is conveniently effected by treating the appropriate compound with a reducing agent such as lithium aluminium hydride in an appropriate solvent, e.g. diethyl ether or tetrahydrofuran, or mixtures thereof.

The compounds of formulae XVII and XVIII above may suitably be prepared by reacting the appropriate compound of formula XI or XIV with a compound of formula XIX:



(XIX)

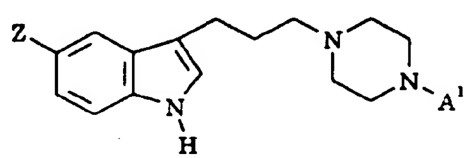
wherein Z is as defined above, and J represents a reactive carboxylate moiety.

Suitable values for the reactive carboxylate moiety J include esters, for example C_{1-4} alkyl esters; acid anhydrides, for example mixed anhydrides with C_{1-4} alkanoic acids; acid halides, for example acid chlorides; and acylimidazoles.

By way of example, the intermediates of formula XIX above wherein J is an acid chloride moiety may be prepared by treating the corresponding carboxylic acid derivative with thionyl chloride in toluene. Similarly, the

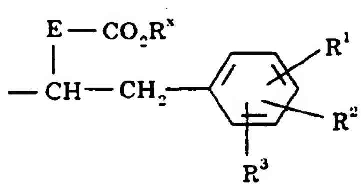
intermediates of formula XIX wherein J is an acylimidazole moiety may be prepared by treating the corresponding carboxylic acid derivative with 1,1'-carbonyldiimidazole. Alternatively, the reactive carboxylate moiety J may be obtained by treating the corresponding compound wherein J is carboxy with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, optionally in the presence of triethylamine; the resulting activated carboxylate intermediate may then suitably be reacted *in situ* with the required compound of formula XI or XIV.

In a still further procedure, the compounds of formula I above wherein R^4 or R^5 represents hydroxy(C_{1-6})alkyl may be prepared by a process which comprises reducing a compound of formula XX:

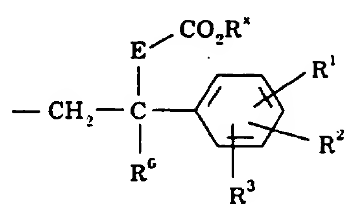


(XX)

wherein Z is as defined above, and A^1 represents a group of formula (iii) or (iv):



(iii)



(iv)

in which E represents a chemical bond or a C_{1-5} alkylene chain, R^x represents C_{1-6} alkyl, and R^1, R^2, R^3 and R^6 are as defined above.

The reduction of the ester functionality in compound XX may conveniently be effected by treatment with a reducing agent such as lithium aluminium hydride, typically in a solvent such as diethyl ether or tetrahydrofuran, or mixtures thereof.

The hydrazine derivatives of formula VII above can be prepared by the methods described in EP-A-0497512 and WO 94/03446, as also can the aniline derivatives of formula XVI.

Where they are not commercially available, the starting materials of formula IV, VA, VB, VI, X, XI, XIV, XIX and XX may be prepared by methods analogous to those described in the accompanying Examples, or by standard procedures well known from the art.

It will be understood that any compound of formula I initially obtained from any one of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I wherein R^4 or R^5 is hydroxy(C_{1-6})alkyl initially obtained may be treated with mesyl chloride under standard conditions to obtain the corresponding mesylate, which in turn may be converted into the desired compound of formula I wherein R^4 or R^5 represents C_{1-6} alkoxy(C_{1-6})alkyl by reaction with the appropriate C_{1-6} alkoxide salt, for example sodium methoxide, typically in methanol/tetrahydrofuran with heating under sealed tube conditions.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such

as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with the present invention potently and selectively bind to the 5-HT_{1D_α} receptor subtype, inhibit forskolin-stimulated adenylyl cyclase activity, and stimulate [^{35}S]-GTPγS binding to membranes from clonal cell lines expressing human cloned receptors.

5-HT_{1D_α}/5-HT_{1D_β} Radioligand Binding

Chinese hamster ovary (CHO) clonal cell lines expressing the human 5-HT_{1D_α} and 5-HT_{1D_β} receptors were harvested in PBS and homogenised in ice cold 50 mM Tris-HCl (pH 7.7 at room temperature) with a Kinematica polytron and centrifuged at 48,000g at 4°C for 11 min. The pellet was then resuspended in 50 mM Tris-HCl followed by a 10 min incubation at 37°C. Finally the tissue was recentrifuged at 48,000g, 4°C for 11 min and the pellet resuspended, in assay buffer (composition in mM: Tris-HCl 50, pargyline 0.01, $CaCl_2$ 4; ascorbate 0.1%; pH 7.7 at room temperature) to give the required volume immediately prior to use (0.2 mg

protein/ml). Incubations were carried out for 30 min at 37°C in the presence of 0.02-150 nM [^{3}H]-5-HT for saturation studies or 2-5 nM [^{3}H]-5-HT for displacement studies. The final assay volume was 1 ml. 5-HT (10 μM) was used to define non-specific binding. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters (presoaked in 0.3% PEI/ 0.5% Triton X) followed by 2 x 4 ml washings with 50 mM Tris-HCl. The radioactive filters were then counted on a LKB beta or a Wallac beta plate counter. Binding parameters were determined by non-linear, least squares regression analysis using an iterative curve fitting routine, from which IC_{50} (the molar concentration of compound necessary to inhibit binding by 50%) values could be calculated for each test compound. The IC_{50} values for binding to the 5-HT_{1D_α} receptor subtype obtained for the compounds of the accompanying Examples were below 50 nM in each case. Furthermore, the compounds of the accompanying Examples were all found to possess a selective affinity for the 5-HT_{1D_α} receptor subtype of at least 10-fold relative to the 5-HT_{1D_β} subtype.

5-HT_{1D_α}/5-HT_{1D_β} Adenylyl Cyclase Assay

Studies were performed essentially as described in *J. Pharmacol. Exp. Ther.*, 1986, **238**, 248. CHO clonal cell lines expressing the human cloned 5-HT_{1D_α} and 5-HT_{1D_β} receptors were harvested in PBS and homogenised, using a motor driven teflon/glass homogeniser, in ice cold Tris HCl-EGTA buffer (composition in mM: Tris HCl 10, EGTA 1, pH 8.0 at room temperature) and incubated on ice for 30-60 min. The tissue was then centrifuged at 20,000g for 20 min at 4°C, the supernatant discarded and the pellet resuspended in Tris HCl-EDTA buffer (composition in mM: Tris HCl 50, EDTA 5, pH 7.6 at room temperature) just prior to assay. The adenylyl cyclase activity was determined by measuring the conversion of α-[^{33}P]-ATP to [^{33}P]-cyclic AMP. A 10 μl aliquot of the membrane

suspension was incubated, for 10-15 min. in a final volume of 50 µl, at 30°C, with or without forskolin (10 µM), in the presence or absence of test compound. The incubation buffer consisted of 50 mM Tris HCl (pH 7.6 at room temperature), 100 mM NaCl, 30 µM GTP, 50 µM cyclic AMP, 1 mM dithiothreitol, 1 mM ATP, 5 mM $MgCl_2$, 1 mM EGTA, 1 mM 3-isobutyl-1-methylxanthine, 3.5 mM creatinine phosphate, 0.2 mg/ml creatine phosphokinase, 0.5-1 µCi α-[^{33}P]-ATP and 1 nCi [^{3}H]-cyclic AMP. The incubation was initiated by the addition of membrane, following a 5 min preincubation at 30°C, and was terminated by the addition of 100 µl SDS (composition in mM: sodium lauryl sulphate 2%, ATP 45, cyclic AMP 1.3, pH 7.5 at room temperature). The ATP and cyclic AMP were separated on a double column chromatography system (*Anal. Biochem.*, 1974, **58**, 541). Functional parameters were determined using a least squares curve fitting programme ALLFIT (*Am. J. Physiol.*, 1978, **235**, E97) from which E_{max} (maximal effect) and EC_{50} (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC_{50} values for the 5-HT_{1D_α} receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT_{1D_α} receptor subtype relative to the 5-HT_{1D_β} subtype.

5-HT_{1D_α}/5-HT_{1D_β} GTPγS Binding

Studies were performed essentially as described in *Br. J. Pharmacol.*, 1993, **109**, 1120. CHO clonal cell lines expressing the human cloned 5-HT_{1D_α} and 5-HT_{1D_β} receptors were harvested in PBS and homogenised using a Kinematica polytron in ice cold 20 mM HEPES containing 10 mM EDTA, pH 7.4 at room temperature. The membranes were then centrifuged at 40,000g, 4°C for 15 min. The pellet was then

resuspended in ice cold 20 mM HEPES containing 0.1 mM EDTA, pH 7.4 at room temperature and recentrifuged at 40,000g, 4°C for 15-25 minutes. The membranes were then resuspended in assay buffer (composition in mM: HEPES 20, NaCl 100, $MgCl_2$ 10, pargyline 0.01; ascorbate 0.1%; pH 7.4 at room temperature) at a concentration of 40 µg protein/ml for the 5-HT_{1D_α} receptor transfected cells and 40-50 µg protein/ml for the 5-HT_{1D_β} receptor transfected cells. The membrane suspension was then incubated, in a volume of 1 ml, with GDP (100 µM for 5-HT_{1D_α} receptor transfected cells, 30 µM for the 5-HT_{1D_β} receptor transfected cells) and test compound at 30°C for 20 min and then transferred to ice for a further 15 min. [^{35}S]-GTPγS was then added at a final concentration of 100 pM and the samples incubated for 30 min at 30°C. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters and washed with 5 ml water. The radioactive filters were then counted on a LKB beta counter. Functional parameters were determined by a non-linear, least squares regression analysis using an iterative curve fitting routine, from which E_{max} (maximal effect) and EC_{50} (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC_{50} values for the 5-HT_{1D_α} receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT_{1D_α} receptor subtype relative to the 5-HT_{1D_β} subtype.

EXAMPLE 1

(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(3-hydroxy-2-phenylpropyl)piperazine. 1.6 Hydrogen Oxalate. 0.4 Diethyl etherate

1. Intermediate 1: 3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propan-1-ol

a) 4-(1,2,4-Triazol-4-yl)phenylhydrazine

Prepared as described in WO 94/03446, Example 1.

b) 3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propan-1-ol

A solution of 4-(1,2,4-triazol-4-yl)phenylhydrazine (25g, 143mmol) in dioxan (250ml) was treated with dihydropyran (24g, 286mmol) followed by 1M hydrochloric acid (150ml) and heated at reflux for 18 hours. The reaction mixture was evaporated with toluene then reevaporated. Inorganic solids were removed by treating the residue with a mixture of methanol and acetonitrile. The mother liquors were purified by column chromatography on silica using dichloromethane:methanol (9:1 → 4:1) as the eluant. The compound was recrystallised from acetonitrile to afford the title compound as a white solid (10.24g, 30%), mp 205-207°C. δ (360 MHz, d_6-DMSO) 1.81 (2H, quintet, J=7Hz, CH_2), 2.75 (2H, t, J=8Hz, CH_2), 3.46 (2H, dt, J_1=6Hz, J_2=5Hz, CH_2), 4.43 (1H, t, J=5Hz, OH), 7.26 (1H, d, J=2Hz, Ar-H), 7.29 (1H, dd, J_1=9Hz, J_2=2Hz, Ar-H), 7.47 (1H, d, J=9Hz, Ar-H), 7.77 (1H, d, J=2Hz, Ar-H), 9.01 (2H, s, Triazole-H), 11.05 (1H, br s, indole NH). MS, CI^+, m/z for $(M+H)^+$=243.

2. Intermediate 2: (±)-1-*tert*-Butyloxycarbonyl-4-(3-hydroxy-2-phenylpropyl)piperazine

a) (±)-Methyl 2-(phenyl)-3-[4-(*tert*-butyloxycarbonyl)piperazin-1-yl]propionate

Methyl 2-(phenyl)propenoate was prepared using the procedures described by Howard, A.S. *et al.* in *J. Org. Chem.*, **1980**, *45*, 1713-1715. *tert*-Butyl 1-piperazinecarboxylate (4.25g, 23.0mmol) and a catalytic quantity of sodium hydroxide (0.18g) were added successively to a stirred solution of methyl 2-(phenyl)propenoate (3.70g, 23.0mmol), in anhydrous THF (50ml). The mixture was stirred at +25°C for 16h and then at 50-60°C for 6h before partitioning between ethyl acetate and water. The organic layer was separated and washed with water (x2) and brine (x2), and dried ($MgSO_4$). The solvent was removed under vacuum and the residue chromatographed on silica gel eluting with ethyl acetate/hexane (30:70) to give the title-*piperazine* (5.10g, 65%), δ (250MHz, $CDCl_3$) 1.45 (9H, s, $(Me)_3$), 2.33-2.58 (5H, m, 2 of CH_2 and CH of CH_2), 3.19 (1H, dd, J=12.6 and 10.4Hz, CH of CH_2), 3.38 (4H, br s, 2 of CH_2), 3.68 (3H, s, CO_2*Me*), 3.84 (1H, dd, J=10.4 and 4.9Hz, CH), 7.22-7.33 (5H, m, Ar-H).

b) <u>(±)-1-*tert*-Butyloxycarbonyl-4-(3-hydroxy-2-phenylpropyl)piperazine</u>

To a stirred solution of the preceding ester (2.5g, 7.20mmol), in anhydrous THF (100ml), cooled to -60°C, was added diisobutylaluminium hydride (18ml of a 1.0M solution in THF, 18.0mmol) and the mixture stirred for 0.5h before warming to +25°. After 4h the reaction mixture was quenched by successive addition of methanol (3ml), water (15ml) and 4N NaOH solution (10ml). The precipitated aluminium salts were removed by filtration and washed with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:1) to give the title-*alcohol* (0.55g, 26%), δ (250MHz, $CDCl_3$) 1.46 (9H, s, $(Me)_3$), 2.36-2.46 (2H, m, CH_2), 2.66-2.79 (3H, m, CH and CH_2), 2.97-3.04 (1H, m, CH of CH_2), 3.23-3.29 (1H, m, CH of CH_2), 3.42-3.56 (4H, m, 2 of CH_2), 3.82-3.87 (1H, m, CH of CH_2), 3.95-4.01 (1H, m, CH of CH_2), 7.15-7.33 (5H, m, Ar-H).

3. (±)-1-*H*-4-(3-Hydroxy-2-phenylpropyl)piperazine

A solution of the preceding N-Boc piperazine (0.55g, 1.72mmol) in 90% formic acid (15ml) was stirred at room temperature for 16h. The solvent was evaporated *in vacuo* and the residue neutralised by addition of aqueous K_2CO_3 (5ml). The mixture was partitioned between water (15ml) and n-butanol (50ml x 2). The organics were combined, the solvent removed under vacuum, and the residue chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (20:8:1) to give the desired NH-piperazine (0.11g, 30%).

4. (±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(3-hydroxy-2-phenylpropyl)piperazine 1.6 Hydrogen Oxalate 0.4 Diethyl etherate

To a solution of Intermediate 1 (0.20g, 0.83mmol) in anhydrous THF (100ml), at 0°C, was added triethylamine (0.167g, 1.65mmol) and methane sulphonyl chloride (0.19g, 1.65mmol) and the mixture warmed to room temperature and stirred for 1.5h. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (50ml) and K_2CO_3 solution (10ml). The aqueous was separated and extracted further with ethyl acetate (1x50ml). The combined extracts were dried ($MgSO_4$) and evaporated and used in the next step without further purification. To a solution of the preceding mesylate (0.264g, 0.825mmol), in isopropyl alcohol (25ml), was added powdered K_2CO_3 (0.114g, 0.825mmol), sodium iodide (82mg, 0.55mmol) and (±)-1-*H*-4-(3-hydroxy-2-phenylpropyl)-piperazine (0.11g, 0.55mmol), and the mixture stirred at 120°C for 16h. The mixture was cooled to room temperature and the solvent removed *in vacuo*. The residue was partitioned between aq. K_2CO_3 solution (5ml) and ethyl acetate (x3). The combined extracts were dried ($MgSO_4$) and evaporated, and the residue chromatographed through silica gel eluting with CH_2Cl_2/MeOH/NH_3 (90:8:1) to give the title-*indole* (0.104g, 43%). The 1.6 hydrogen oxalate salt was prepared, mp 137-140°C, (Found: C, 59.62;

H, 6.67; N, 13.36. $C_{26}H_{32}N_6O$. 1.6 ($C_2H_2O_4$). 0.4 ($C_4H_{10}O$) requires C, 59.83; H, 6.39; N, 13.59%), m/e 445 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.92-2.06 (2H, m, CH_2), 2.56-3.62 (17H, m, 8 of CH_2 and CH), 7.18-7.34 (7H, m, Ar-H), 7.50 (1H, d, J=8.6Hz, Ar-H), 7.79 (1H, s, Ar-H), 9.01 (2H, s, Ar-H), 11.17 (1H, s, NH).

EXAMPLE 2

(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(3-methoxy-2-phenylpropyl)piperazine. Sesquioxalate 0.6 Hydrate 0.2 Diethyl etherate

a) (±)-1-*tert*-Butoxycarbonyl-4-(3-methoxy-2-phenylpropyl)piperazine

To a solution of Intermediate 2 (0.60g, 1.88mmol) in anhydrous DMF (20ml), at 0°C, was added sodium hydride (0.113g of a 60% dispersion in oil, 2.81mmol) and the mixture stirred for 0.2h, before adding methyl iodide (0.399g, 2.81mmol), dropwise. The mixture was warmed to room temperature, stirred for 2h, and then partitioned between water and ethyl acetate. The organic phase was separated and washed with water (x2) and brine (x1). After drying ($MgSO_4$), the solvent was removed *in vacuo* and the crude product chromatographed through silica gel eluting with ethyl acetate/hexane (1:1) to give the desired methyl ether (0.365g, 60%), δ (250MHz, $CDCl_3$) 1.44 (9H, s, $(Me)_3$), 2.26-2.78 (6H, m, 3 of CH_2), 3.02-3.16 (1H, m, CH), 3.31 (3H, s, OMe), 3.34-3.40 (4H, m, 2 of CH_2), 3.53-3.69 (2H, m, CH_2), 7.19-7.34 (5H, m, Ar-H).

b) (±)-1-*H*-4-(3-Methoxy-2-phenylpropyl)piperazine

Prepared from the preceding N-Boc piperazine using the procedure described for Example 1 step 3 (81% yield), δ (360MHz, $CDCl_3$) 2.30-2.52 (5H, m, 2 of CH_2 and CH of CH_2), 2.67 (1H, dd, J=12.7 and 7.8Hz, CH of CH_2), 2.81-2.84 (4H, m, 2 of CH_2), 3.07-3.15 (1H, m, CH), 3.30 (3H, s,

OMe), 3.56 (1H, dd, J=9.3 and 7.3Hz, CH of CH_2), 3.67 (1H, dd, J=9.3 and 5.7Hz, CH of CH_2), 7.18-7.32 (5H, m, Ar-H).

c) (±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(3-methoxy-2-phenylpropyl)piperazine. Sesquioxalate 0.6 Hydrate 0.2 Diethyl etherate

The title-compound was prepared from the mesylate of Intermediate 1 and 1*H*-4-(3-methoxy-2-phenylpropyl)piperazine using the coupling procedure described for Example 1 step 4. The sesquioxalate salt was prepared, mp 134-136°C, (Found: C, 59.56; H, 6.56; N, 13.85. $C_{27}H_{34}N_6O$. 1.5 ($C_2H_2O_4$). $0.6H_2O$. 0.2 ($C_4H_{10}O$) requires C, 59.74; H, 6.54; N, 13.57%), m/e 459 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.92-2.05 (2H, m, CH_2), 2.50-3.16 (15H, m, 7 of CH_2 and CH), 3.19 (3H, s, OMe), 3.45-3.57 (2H, m, CH_2), 7.17-7.34 (7H, m, Ar-H), 7.50 (1H, d, J=8.7Hz, Ar-H), 7.79 (1H, d, J=2.0Hz, Ar-H), 9.02 (2H, s, Ar-H), 11.17 (1H, s, NH).

EXAMPLE 3

(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)-3-hydroxypropyl]piperazine. 1.3 Hydrogen Oxalate. 0.5 Diethyl etherate

1. Intermediate 3: 1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(*H*)-piperazine

a) 5-Bromopentanal dimethyl acetal

To a solution of 5-bromovaleryl chloride (50g, 0.251mol) in anhydrous THF (500ml), at -78°C, was added lithium tri-*tert*-butoxyaluminohydride (1.0M solution in tetrahydrofuran, 300ml: 0.30mol), keeping the temperature below -70°C. The solution was stirred at -78°C for 5h and then quenched by dropwise addition of 2M hydrochloric acid (350ml). The mixture was warmed to room temperature and stirred for 16h. Diethyl ether (500ml) was added, the aqueous phase

separated and extracted further with ether (x 2). The combined extracts were washed with saturated Na_2CO_3 solution (x 1), water (x 1) and brine (x 2), dried (Na_2SO_4) and evaporated to give 5-bromovaleraldehyde (37.5g, 91%). A solution of 5-bromovaleraldehyde (37.5g, 0.227mol) in methanol (250ml) and concentrated sulphuric acid (0.5ml) was stirred at room temperature for 3h. The solvent was removed under vacuum and to the residue was added K_2CO_3 solution (50ml) and diethyl ether (500ml). The aqueous layer was separated and re-extracted with ether (x 2). The combined extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. The crude product was chromatographed on silica gel eluting with diethyl ether/hexane (1:9) to give the title-acetal (27.5g, 57%). δ (250MHz, $CDCl_3$) 1.43-1.67 (4H, m, 2 of CH_2); 1.83-1.94 (2H, m, CH_2); 3.38 (6H, s, $CH(OMe)_2$); 3.42 (2H, t, J = 7Hz, CH_2Br), 4.37 (1H, t, J = 7Hz, $C\underline{H}(OMe)_2$).

b) <u>5-[4-(*tert*-Butyloxycarbonyl)piperazin-1-yl]pentanal dimethyl acetal</u>

A mixture of 5-bromovaleraldehyde dimethyl acetal (27.5g, 0.13mol), Na_2CO_3 (20.7g, 0.195mol), sodium iodide (19.5g, 0.13mol) and *tert*-butyl 1-piperazinecarboxylate (25.5g, 0.137mol), in dimethoxyethane (250ml), was heated at 100°C for 3h. Aluminium foil was wrapped around the vessel to exclude light. The mixture was cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure and then EtOAc (50ml) added and the mixture filtered again to remove inorganic salts. The solvent was removed under vacuum and the residue chromatographed on silica gel eluting with EtOAc to give the title-product (25.7g, 63%). δ (250MHz, $CDCl_3$) 1.29-1.71 (6H, m, 3 of CH_2): 1.46 (9H, s, $OC(Me)_3$); 2.31-2.39 (6H, m, 3 of CH_2); 3.32 (6H, s, $CH(O\underline{Me})_2$); 3.41-3.45 (4H, m, 2 of CH_2); 4.36 (1H, t, J = 6Hz, $C\underline{H}(OMe)_2$).

c) 1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(*H*)-piperazine

A mixture of 4-(1,2,4-triazol-4-yl)phenylhydrazine (5.0g, 28.6mmol) and 5-[4-(*tert*-butyloxycarbonyl)piperazin-1-yl]pentanal dimethyl acetal (9.03g, 28.6mmol) in 4% sulphuric acid (150ml) was heated at reflux for 48h. The solution was cooled in an ice-bath, basified with solid K_2CO_3 and extracted with butan-1-ol (x 3). The solvent was removed under vacuum and azeotroped with hexane (x 2). The crude product was purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (30:8:1) to give the title-indole (3.9g, 44%). δ (360MHz, oxalate salt in D_2O) 2.12-2.24 (2H, m, CH_2); 2.93 (2H, t, J = 7Hz, CH_2); 3.46-3.76 (8H, m, 4 of CH_2); 7.37 (1H, dd, J = 1.9 and 8.7Hz, Ar-H); 7.39 (1H, s, Ar-H); 7.66 (1H, d, J = 8.7, Ar-H); 7.82 (1H, d, J = 1.9Hz, Ar-H); 9.13 (2H, s, Triazole-H).

2. (±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)-2-(methoxycarbonyl)ethyl]piperazine

Methyl 2-(4-fluorophenyl)propenoate was prepared using the procedures described by Howard, A.S. *et al.* in *J. Org. Chem.*, **1980**, *45*, 1713-1715. Intermediate 3 (0.308g, 0.992mmol) and sodium hydroxide (catalytic amount, 19mg) were added successively to a stirred solution of methyl 2-(4-fluorophenyl)propenoate (0.179g, 0.994mmol), in methanol (5ml). The mixture was stirred at 60°C for 4.5h and the solvent then removed *in vacuo*. The residue was partitioned between ethyl acetate and water, and the organic layer separated and washed with water and brine. After drying ($MgSO_4$), the solvent was removed *in vacuo* and the crude product was chromatographed through silica gel eluting with CH_2Cl_2/MeOH (9:1) to give the title-*product* (0.244g, 50%), δ (250MHz, $CDCl_3$) 1.82-2.01 (2H, m, CH_2), 2.34-2.81 (13H, m, 6 of CH_2 and CH of CH_2), 3.14 (1H, dd, J=12.6 and 10.2Hz, CH of CH_2), 3.67 (3H, s, CO_2*Me*), 3.81 (1H, dd, J=10.2 and 5.1Hz, CH), 6.96-7.31 (6H, m, Ar-H), 7.48 (1H, d, J=8.5Hz, Ar-H), 7.56 (1H, d, J=2.0Hz, Ar-H), 8.47 (2H, s, Ar-H), 8.50 (1H, br s, NH).

3. (±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)-3-hydroxypropyl]piperazine. 1.3 Hydrogen Oxalate 0.5 Diethyl etherate

Lithium aluminium hydride (0.39ml of a 1.0M solution in THF, 0.39mmol) was added dropwise to a stirred solution of the preceding methyl ester (0.192g, 0.391mmol), in anhydrous THF (10ml), at -17°C. The mixture was stirred at -20°C for 2h and a further portion of $LiAlH_4$ (0.2ml of a 1.0M solution in THF, 0.2mmol) then added. After 1h the reaction mixture was quenched by addition of saturated Na_2SO_4 solution (0.6ml) and the resulting precipitate was removed by filtration through celite. The solvent was removed *in vacuo* and the residue chromatographed through silica gel eluting with CH_2Cl_2/MeOH/NH_3 (60:8:1) to give the title-*alcohol* (0.152g, 84%). The 1.3 hydrogen oxalate salt was prepared, mp 138-140°C (Found: C, 59.39; H, 6.56; N, 13.40. $C_{26}H_{31}N_6FO$. 1.3 ($C_2H_2O_4$). 0.5 ($C_4H_{10}O$) requires C, 59.60; H, 6.31; N, 13.63%), m/e 463 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.92-2.04 (2H, m, CH_2), 2.52-3.08 (15H, m, 7 of CH_2 and CH), 3.49-3.60 (2H, m, CH_2), 7.06-7.11 (2H, m, Ar-H), 7.26-7.33 (4H, m, Ar-H), 7.49 (1H, d, J=8.7Hz, Ar-H), 7.78 (1H, d, J=2.0Hz, Ar-H), 9.00 (2H, s, Ar-H), 11.16 (1H, s, NH).

EXAMPLE 4

(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)prop-2-yl]piperazine. 3.0 Hydrogen Oxalate. 1.5 Hydrate

To a solution of Intermediate 3 (0.310g, 1.0mmol), in MeOH (30ml), was added 4-fluorophenyl acetone (0.197g, 1.3mmol), glacial acetic acid (0.28ml, 5.0mmol) and sodium cyanoborohydride (0.158g, 2.5mmol), and the mixture stirred at room temperature for 16h. Further portions of sodium cyanoborohydride (0.316g, 5.0mmol) and glacial acetic acid (0.56ml, 10mmol) were added and the mixture stirred for 2h. The solvent

was removed *in vacuo* and the residue partitioned between ethyl acetate (x3) and saturated K_2CO_3 solution. The organic layer was dried (Na_2SO_4) and evaporated under vacuum, and the residue chromatographed through silica gel eluting with CH_2Cl_2/MeOH (9:1) to give the title-*phenethylpiperazine* (0.065g, 15%). The 3.0 hydrogen oxalate salt was prepared, mp 170-173°C, (Found: C, 51.53; H, 5.53; N, 11.38. $C_{26}H_{31}N_6F$. 3.0 ($C_2H_2O_4$). 1.5 H_2O requires C, 51.68; H, 5.42; N, 11.30%), m/e 447 $(M+1)^+$, δ (360MHz on free base, $CDCl_3$) 1.01 (3H, d, J=4.5Hz, Me), 2.02-2.12 (2H, m, CH_2), 2.42-2.48 (1H, m, CH of CH_2), 2.70-3.06 (13H, m, 6 of CH_2 and CH of CH_2), 3.38-4.00 (1H, m, CH), 6.95-6.99 (2H, m, Ar-H), 7.10-7.15 (3H, m, Ar-H), 7.24 (1H, s, Ar-H), 7.49 (1H, d, J=8.5Hz, Ar-H), 7.57 (1H, d, J=2.0Hz, Ar-H), 8.52 (2H, s, Ar-H).

EXAMPLE 5

(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine. 3.0 Hydrogen Oxalate. Monohydrate

a) (±)-2-(4-Fluorophenyl)propyl bromide

Lithium aluminium hydride (29.8ml of a 1.0M solution in THF, 29.8mmol) was added dropwise to a stirred solution of 4-fluoro-α-methylphenyl acetic acid (5.0g, 29.8mmol), in diethyl ether (100ml), which had been cooled to -10°C. The mixture was warmed to +25°C and stirred for 1h before quenching with methanol (20ml) and 4M NaOH (20ml). The mixture was filtered and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with dichloromethane to give 2-(4-fluorophenyl)propyl alcohol (3.65g, 79%). To a solution of the preceding alcohol (3.65g, 23.7mmol) and carbon tetrabromide (9.82, 29.62mmol), in dichloromethane (75ml), was added triphenylphosphine (9.31g, 35.5mmol), portionwise. The mixture was stirred for 1h at room temperature and diethyl ether (50ml) then added. The precipitated triphenylphosphine

oxide was filtered off and the solvents removed *in vacuo*. The residue was chromatographed through silica gel eluting with ethyl acetate/hexane (1:2) to afford the desired bromide (3.05g, 60%), δ (250MHz, $CDCl_3$) 1.40 (3H, d, J=6.8Hz, Me), 3.06-3.20 (1H, m, CH), 3.42-3.61 (2H, m, CH_2), 6.97-7.26 (4H, m, Ar-H).

b) <u>(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine. 3.0 Hydrogen Oxalate. Monohydrate</u>

A mixture of Intermediate 3 (0.31g, 1.0mmol), 2-(4-fluorophenyl)propyl bromide (0.228g, 1.05mmol), triethylamine (0.202g, 2.0mmol) and sodium iodide (0.165g, 1.1mmol), in DMF (20ml) was heated at 90°C, with stirring, for 16h. The mixture was cooled to room temperature and partitioned between dichloromethane and water. The CH_2Cl_2 layer was separated, dried (Na_2SO_4) and evaporated under vacuum. The crude product was chromatographed through silica gel eluting with CH_2Cl_2/MeOH/NH_3 (90:10:1) to give the title-*indole* (0.125g, 28%). The 3.0 hydrogen oxalate monohydrate salt was prepared, mp 203-205°C, (Found: C, 52.11; H, 5.60; N, 11.45. $C_{26}H_{31}N_6F$. 3.0 ($C_2H_2O_4$). 1.0H_2O requires C, 52.31; H, 5.35; N, 11.44%), δ (360MHz, D_6-DMSO) 1.17 (3H, d, J=6.8Hz, Me), 1.92-2.06 (2H, m, CH_2), 2.44-3.26 (15H, m, 7 of CH_2 and CH), 7.08-7.13 (2H, m, Ar-H), 7.26-7.33 (4H, m, Ar-H), 7.50 (1H, d, J=8.6Hz, Ar-H), 7.78 (1H, d, J=1.5Hz, Ar-H), 9.01 (2H, s, Ar-H), 11.16 (1H, s, NH).

<u>EXAMPLE 6</u>

<u>(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-hydroxyprop-2-yl]piperazine. Sesquioxalate 1.1 Hydrate</u>

a) <u>(±)-2-Bromo-3-(4-fluorophenyl)propionic acid</u>

To a cooled (0°C, ice/salt bath) solution of DL-4-fluorophenylalanine (5.0g, 27.0mmol) and potassium bromide (10.65g, 90.0mmol) in 3M sulphuric acid (45ml) was added sodium nitrite (2.64g, 38.0mmol) portionwise over a 0.5h period. The mixture was stirred at 0°C for 1h and then at room temperature for 1h. The mixture was diluted with water (50ml) and extracted with ether (2x75ml). The combined extracts were washed with water (2x75ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (95:5:1) to give the title-*acid* (3.77g, 56%), δ (250MHz, $CDCl_3$) 3.22 (1H, dd, J=14.3 and 7.2Hz, CH of CH_2), 3.43 (1H, dd, J=14.3 and 8.1Hz, CH of CH_2), 4.38 (1H, dd, J=7.2 and 8.1Hz, CH), 6.98-7.31 (4H, m, Ar-H).

b) (±)-Methyl 2-bromo-3-(4-fluorophenyl)propionate

To a solution of the preceding acid (2.0g, 8.1mmol), in anhydrous methanol (15ml), at -5°C, was added thionyl chloride (1.6g, 13.8mmol), dropwise. The mixture was stirred at -5°C for 0.1h and then at room temperature for 0.5h. The solvent was removed *in vacuo* and the resulting residue azeotroped with toluene (2x10ml) before chromatographing through silica gel using CH_2Cl_2→CH_2Cl_2/MeOH (100→80:20) as eluant. The title-*ester* was isolated as a colourless oil (1.36g, 64%), δ (250MHz, $CDCl_3$) 3.22 (1H, dd, J=14.2 and 7.1Hz, CH of CH_2), 3.43 (1H, dd, J=14.2 and 8.3Hz, CH of CH_2), 3.74 (3H, s, CO_2*Me*), 4.36 (1H, dd, J=8.3 and 7.1Hz, CH), 6.96-7.26 (4H, m, Ar-H).

c) (±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(methoxycarbonyl)-2-(4-fluorophenyl)ethyl]piperazine

To a stirred solution of the preceding bromide (0.287g, 1.1mmol), in anhydrous DMF (5ml), was added Intermediate 3 (0.31g, 1.0mmol) and K_2CO_3 (0.152g, 1.1mmol). The mixture was heated at 50°C for 0.75h and a

further portion of bromide (0.287g, 1.1mmol), as a solution in DMF (2ml), was then added. The mixture was heated for a further 0.5h and then cooled to room temperature and the solvent removed *in vacuo*. The resulting residue was partitioned between CH_2Cl_2 (2x25ml) and water (50ml) and the combined organics were dried (Na_2SO_4) and evaporated under vacuum. The residue was chromatographed through silica gel eluting with CH_2Cl_2/MeOH (90:10→80:20) to give the title-*indole* (0.224g, 46%) as a yellow foam, δ (360MHz, $CDCl_3$) 1.89-1.98 (2H, m, CH_2), 2.44-2.82 (12H, m, 6 of CH_2), 2.90 (1H, dd, J=13.5 and 6.0Hz, CH of CH_2), 3.02 (1H, dd, J=13.5 and 9.4Hz, CH of CH_2), 3.39 (1H, dd, J=9.4 and 6.0Hz, CH), 3.59 (3H, s, CO_2*Me*), 6.92-6.97 (2H, m, Ar-H), 7.11-7.16 (4H, m, Ar-H), 7.48 (1H, d, J=8.4Hz, Ar-H), 7.56 (1H, d, J=2.0Hz, Ar-H), 8.43 (1H, br s, NH), 8.47 (2H, s, Ar-H), m/e 491 $(M+1)^+$.

d) <u>(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-hydroxyprop-2-yl]piperazine Sesquioxalate. 1.1 Hydrate</u>

To a cooled (-10°C, dry ice/acetone bath) solution of the preceding indole (0.22g, 0.45mmol), in anhydrous THF (10ml), was added $LiAlH_4$ (0.45ml of a 1.0M solution in diethyl ether, 0.45mmol) dropwise. After stirring at -10°C for 1h a further portion of $LiAlH_4$ (0.23ml, 0.23mmol) was added and the mixture stirred for 0.5h. Saturated Na_2SO_4 solution (0.7ml) was added dropwise and the mixture warmed to room temperature. The precipitate was removed by filtration, the solvent removed *in vacuo*, and the residue remaining was chromatographed through silica gel eluting with CH_2Cl_2/MeOH/NH_3 (90:10:0→80:20:0→80:20:1) to give the title-*alcohol* (0.137g, 66%). The sesquioxalate monohydrate salt was prepared. mp 104°C (dec.), (Found: C, 56.31; H, 6.15; N, 13.75. $C_{26}H_{31}N_6OF$. 1.5 $(C_2H_2O_4)$. 1.1 H_2O requires C, 56.41; H, 5.91; N, 13.61%), m/e 463 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.92-2.06 (2H, m, CH_2), 2.56-3.12 (15H, m, 7 of CH_2 and CH), 3.36-3.47 (2H, m, CH_2), 7.07-7.12 (2H, m, Ar-H), 7.25-7.34 (4H,

m, Ar-H), 7.51 (1H, d, J=8.6Hz, Ar-H), 7.80 (1H, d, J=1.5Hz, Ar-H), 9.02 (2H, s, Ar-H), 11.17 (1H, s, NH).

EXAMPLE 7

(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-methoxyprop-2-yl]piperazine. Sesquioxalate Hemihydrate

To a solution of Example 6 (0.115g, 0.25mmol) in anhydrous THF (10ml), at 0°C (ice/water bath), was added triethylamine (0.05g, 0.50mmol) and methane sulphonyl chloride (0.057g, 0.50mmol) and the mixture stirred at 0°C for 0.3h and at room temperature for 0.3h. The mixture was added portionwise to a solution of sodium (0.115g, 5.0mmol) in methanol (10ml) and heated in a sealed tube at 75°C for 0.5h. The solvent was then removed *in vacuo* and the residue partitioned between ethyl acetate (2x50ml) and water (50ml). The organics were combined, dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was chromatographed through silica gel eluting with $CH_2Cl_2/MeOH/NH_3$ (95:5:1→90:10:1) to give the title-methyl ether (62mg, 52%). The sesquioxalate hemihydrate salt was prepared. mp 88°C (dec.), (Found: C, 57.96; H, 6.06; N, 13.36. $C_{27}H_{33}N_6FO$. 1.5 ($C_2H_2O_4$). 0.5 (H_2O) requires C, 58.06; H, 6.01; N, 13.54%), m/e 477 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.94-2.08 (2H, m, CH_2), 2.30-3.12 (15H, m, 7 of CH_2 and CH), 3.20 (3H, s, OMe), 3.28-3.38 (2H, s, CH_2), 7.06-7.11 (2H, m, Ar-H), 7.23-7.34 (4H, m, Ar-H), 7.51 (1H, d, J=8.4Hz, Ar-H), 7.80 (1H, d, J=1.5Hz, Ar-H), 9.02 (2H, s, Ar-H), 11.18 (1H, s, NH).

EXAMPLE 8

(±)-1-[3-(5-(Imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(phenyl)propyl]piperazine. 3.0 Hydrogen Maleate. 0.1 Hydrate

1. 1-[3-(5-(Imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-(*H*)-piperazine

a) 4-(Imidazol-1-yl)nitrobenzene

To a stirred solution of imidazole (34.1g, 0.50mol) in DMF (300ml) under Ar, was added portionwise, over 23 minutes, 60% NaH in oil (20.02g, 0.50mol). The mixture was then stirred at room temperature for 18 minutes before adding dropwise, over 40 minutes, a solution of 1-fluoro-4-nitrobenzene (70.62g, 0.50mol) in DMF (60ml). The mixture was then stirred at room temperature overnight. Water (600ml) was then added and the solid was filtered off, washed with water, then stirred in boiling ethyl acetate (400ml), allowed to cool and filtered, washing the solid with more ethyl acetate (50ml), then petroleum ether (250ml). The filtrate, now containing more solid, was refiltered and washed with petroleum ether. The combined solids were dried in a vacuum desiccator overnight to give 90.14g (95%) of the *title compound* as a yellow solid. δ_H (360MHz, DMSO-d_6) 7.19 (1H, t, J=1.1Hz), 7.97-8.03 (3H, m), 8.38 (2H, d, J=9.2Hz), 8.52 (1H, t).

b) 4-(Imidazol-1-yl)aniline. Dihydrochloride

A mixture of 4-(imidazol-1-yl)nitrobenzene (89.60g, 0.474mol) and 10% palladium on carbon (4.50g) in ethanol (1200ml) and 5N HCl (189ml) was hydrogenated in two batches at 40psi for 80 minutes. Water (450ml) was then added to dissolve the product and the catalyst was removed by filtration, washing with more water, and the combined filtrates were evaporated *in vacuo*, using finally a freeze drier, to give 105.4g (96%) of the *title compound* as a cream solid. δ_H (250MHz, D_2O) 7.22 (2H, d, J=8.8Hz), 7.35 (1H, t, J=2.1Hz), 7.44 (2H, d, J=9.0Hz), 7.59 (1H, t, J=1.8Hz), 8.89 (1H, t, J=1.5Hz).

c) 4-(Imidazol-1-yl)phenylhydrazine. Dihydrochloride

To a cooled (-15°C) and stirred suspension of 4-(imidazol-1-yl)aniline dihydrochloride (20g, 86.16mmol) in concentrated hydrochloric acid (100ml) was added dropwise, over 1 hour, a solution of sodium nitrite (6.25g, 9.05mmol) in water (40ml). After a further 10 minutes of stirring at -12°C, the mixture was quickly filtered to remove a solid, and the filtrate was added portionwise to a cooled (-20°C) and stirred solution of tin (II) chloride dihydrate (100g) in concentrated hydrochloric acid (50ml) at such a rate as to maintain the internal temperature below -10°C (15 minutes). The mixture was allowed to warm to 5°C over 30 minutes, and the solid was collected and washed with diethyl ether (4 x 100ml). The above solid was suspended in water (200ml) and basified with 4N sodium hydroxide solution and extracted with ethyl acetate (5 x 500ml). The combined organic solutions were dried (Na_2SO_4) and filtered. The filtrate was vigorously stirred while hydrogen chloride was being bubbled through the solution until a deep red mixture was obtained. Stirring was continued for a further 20 minutes to give a cream solid which was collected by filtration and dried over phosphorus pentoxide-potassium hydroxide under high vacuum to leave 12.7g (60%) of the *title compound*: δ_H (360MHz, DMSO-d_6) 7.20 (2H, d, J=9.0Hz), 7.73 (2H, d, J=9.0Hz), 7.91 (1H, t, J=1.5Hz), 8.23 (1H, t, J=1.7Hz), 9.71 (1H, t, J=1.3Hz).

d) 1-[3-(5-(Imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-(*H*)-piperazine

Prepared from 4-(imidazol-1-yl)phenylhydrazine and 5-[4-(*tert*-butyloxcarbonyl)piperazin-1-yl]pentanal dimethyl acetal using the procedure described for Example 3, Intermediate 3. δ (250MHz, D_6-DMSO) 1.86-1.97 (2H, m, CH_2), 2.37-3.66 (12H, m, 6 of CH_2), 4.23 (1H, br s, NH), 7.20 (1H, s, Ar-H), 7.35-7.40 (2H, m, Ar-H), 7.56 (1H, d, J=8.6Hz, Ar-H), 7.77 (1H, d, J=2.0Hz, Ar-H), 7.80 (1H, d, J=2.0Hz, Ar-H), 8.24 (1H, s, Ar-H), 11.11 (1H, s, NH).

2. (±)-1-[3-(5-(Imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(phenyl)propyl]piperazine. 3.0 Hydrogen Maleate. 0.1 Hydrate

Sodium cyanoborohydride (78mg, 1.25mmol) was added to a solution of 1-[3-(5-(imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-(*H*)-piperazine (0.308g, 1.0mmol) and glacial acetic acid (0.15g, 2.5mmol), in methanol (40ml) at -10°C. A solution of (±)-2-phenylpropionaldehyde (0.16g, 1.12mmol), in methanol (10ml), was added dropwise and the reaction mixture was warmed to room temperature and stirred for 16h. The solution was basified by addition of saturated K_2CO_3 solution and the methanol was evaporated *in vacuo*. The resulting aqueous was extracted with CH_2Cl_2 (3x100ml) and the combined extracts were dried (Na_2SO_4) and evaporated, and the residue chromatographed on silica gel eluting with 10% methanol/CH_2Cl_2 to give the title-*product* (0.263g, 62%). The 3.0 hydrogen maleate 0.1 hydrate salt was prepared, mp 140-141°C, (Found: C, 59.19; H, 5.96; N, 9.26. $C_{27}H_{33}N_5$ 3.0 ($C_4H_4O_4$). 0.1 H_2O requires C, 60.23; H, 5.86; N, 9.01%), m/e 428 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.19 (3H, d, J=6.9Hz, Me), 1.94-2.06 (2H, m, CH_2), 2.52-3.60 (15H, m, CH and 7 of CH_2), 6.13 (maleate-H's), 7.17-7.39 (7H. m. Ar-H), 7.53 (1H. d. J=8.6Hz. Ar-H), 7.55 (1H, s, Ar-H), 7.83 (1H, d, J=2.0Hz, Ar-H), 7.97 (1H, s. Ar-H). 8.93 (1H, s, Ar-H), 11.19 (1H, s, NH).

EXAMPLE 9

(±)-1-[3-(5-(Imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)-propyl]piperazine. 2.5 Hydrogen Maleate. 0.75 Hydrate

The title *compound* was prepared by alkylation of 1-[3-(5-imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-(*H*)-piperazine with (±)-2-(4-fluorophenyl)-propyl bromide as described for the synthesis of Example 5. The 2.5 hydrogen maleate 0.75 hydrate salt was prepared. mp 137-138°C. (Found: C, 59.29; H, 5.88; N, 9.29. $C_{27}H_{32}N_5F$. 2.5($C_4H_4O_4$). 0.75H_2O requires C,

59.31; H, 5.85; N, 9.35%), m/e 446 $(M+1)^+$, δ (250MHz, $CDCl_3$, free base) 1.23 (3H, d, J=6.9Hz, Me), 1.85-1.97 (2H, m, CH_2), 2.32-2.60 (12H, m, 6 of CH_2), 2.77 (2H, t, J=7.5Hz, CH_2), 2.85-2.98 (1H, m, CH), 6.92-7.21 (7H, m, Ar-H), 7.29 (1H, s, Ar-H), 7.41 (1H, d, J=8.6Hz, Ar-H), 7.56 (1H, d, J=2.0Hz, Ar-H), 7.84 (1H, s, Ar-H), 8.58 (1H, s, NH).

EXAMPLE 10

(±)-1-[3-(5-(1,2,4-Triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine. Dihydrogen Maleate

1. 3-[5-(1,2,4-Triazol-1-ylmethyl)-1*H*-indol-3-yl]propan-1-ol

3,4-Dihydro-2*H*-pyran (3.9ml, 42.7mmol) was added to a stirred solution of 4-(1,2,4-triazol-1-ylmethyl)phenylhydrazine (EP 497,512; 4.0g, 21.1mmol) in dioxane/water/5N HCl (38ml/14ml/4.7ml) and stirred at room temperature for 1.75 h. The solution was then refluxed for 1.5 h and the solvent removed under vacuum. The residue was taken up into CH_2Cl_2 and saturated aqueous K_2CO_3 solution. The aqueous was separated and further extracted with CH_2Cl_2 (x4). The combined organic extracts were dried ($MgSO_4$) and evaporated and the residue chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (80:8:1) to give the title-*indole* (0.919g, 17%), δ (250MHz, $CDCl_3$) 1.91-2.03 (2H, m, CH_2), 2.84 (2H, t, J=7.9Hz, CH_2), 3.73 (2H, t, J=7.9Hz, CH_2), 5.43 (2H, s, CH_2), 7.04 (1H, d, J=2.3Hz, Ar-H), 7.11 (1H, dd, J=2.3 and 8.3Hz, Ar-H), 7.35 (1H, d, J=8.3Hz, Ar-H), 7.58 (1H, s, Ar-H), 7.97 (1H, s, Ar-H), 8.02 (1H, s, Ar-H), 8.18 (1H, s, NH).

2. (±)-4-[2-(4-Fluorophenyl)propyl]piperazine

A mixture of (±)-2-(4-fluorophenyl)propyl bromide (3.03g, 13.96mmol), *N*-Boc-piperazine (2.60g, 13.96mmol), potassium carbonate (3.86g, 27.93mmol) and sodium iodide (2.09g, 13.96mmol), in anhydrous

isopropyl alcohol (100ml) was refluxed for 16h. The inorganics were filtered off and the solvent evaporated *in vacuo*. The resulting residue was partitioned between CH_2Cl_2 (3x150ml) and water (50ml). The combined extracts were dried (Na_2SO_4) and evaporated and the residue chromatographed on silica gel eluting with hexane to give 1.8g (40%) of product. This material was dissolved in 99% formic acid (50ml) and the solution stirred at room temperature for 16h. The solvent was removed under vacuum and the residue basified by addition of saturated K_2CO_3 solution and then extracted with *n*-butanol (100ml). The *n*-butanol was evaporated *in vacuo* and the residue chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (60:8:1) to give the title-*product* (0.34g, 27%), δ (360MHz, $CDCl_3$) 1.24 (3H, d, J=7.0Hz, Me), 2.30-2:46 (6H, m, 3 of CH_2), 2.78-2.98 (5H, m, 2 of CH_2 and CH), 6.94-7.00 (2H, m, Ar-H), 7.12-7.26 (2H, m, Ar-H).

3. <u>(±)-1-[3-(5-(1,2,4-Triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine. Dihydrogen Maleate</u>

The title-*compound* was prepared from (±)-4-[2-(4-fluorophenyl)propyl]piperazine and 3-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]propan-1-ol using the procedure described for Example 1. The dihydrogen maleate salt was prepared, mp 171-172°C, (Found: C, 60.66; H, 5.95; N, 12.11. $C_{27}H_{33}N_6F$. 2.0 ($C_4H_4O_4$) requires C, 60.68: H, 5.97: N, 12.31%), m/e 461 $(M+1)^+$, δ (250MHz, $CDCl_3$, free base) 1.24 (3H, d, J=6.9Hz, Me), 1.83-1.95 (2H, m, CH_2), 2.39-2.56 (12H, m, 6 of CH_2), 2.74 (2H, t, J=7.7Hz, CH_2), 2.85-3.00 (1H, m, CH), 5.42 (2H, s, CH_2), 6.93-7.18 (6H, m, Ar-H), 7.35 (1H, d, J=8.3Hz, Ar-H), 7.57 (1H, s, Ar-H), 7.96 (1H, s, Ar-H), 7.98 (1H, s, Ar-H), 8.10 (1H, br s, NH).

EXAMPLE 11

(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(3-fluorophenyl)-3-methoxypropyl]piperazine. 3.5 Hydrogen Oxalate. 1.5 Diethyl Etherate

The title compound was prepared from 3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]propan-1-ol using the procedures described for Example 2. The 3.5 hydrogen oxalate 1.5 diethyl etherate salt was prepared, mp 145°C (dec.), (Found: C, 53.21; H, 6.14; N, 9.31. $C_{27}H_{33}N_6OF$. 3.5 ($C_2H_2O_4$). 1.5($C_4H_{10}O$) requires C, 53.20; H, 6.06; N, 9.58%), m/e 477 $(M+1)^+$, δ (360MHz. $CDCl_3$. free base) 1.88-2.02 (2H, m, CH_2), 2.42-2.74 (12H, m, 6 of CH_2), 2.78 (2H, t, J=7.4Hz, CH_2), 3.02-3.14 (1H, m, CH), 3.29 (3H, s, OMe), 3.49-3.64 (2H, s, CH_2OMe), 6.88-7.00 (3H, m, Ar-H), 7.13-7.27 (3H, m, Ar-H), 7.46 (1H, d, J=8.5Hz, Ar-H), 7.55 (1H, d, J=2.0Hz, Ar-H), 8.35 (1H, s, NH), 8.46 (2H, s, Ar-H).

EXAMPLE 12

(±)-1-[3-(5-(1,2,3-Triazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine. Dihydrogen Maleate

1. 1-[3-(5-(1,2,3-Triazol-1-yl)-1*H*-indol-3-yl)propyl]-4(*H*)-piperazine

The title *compound* was prepared from 4-(1,2,3-triazol-1-yl)phenyl hydrazine (EP 497,512) and 3,4-dihydro-2*H*-pyran using the procedures described for Example 1. Intermediate 1, δ (250MHz. $CDCl_3$) 1.94-2.05 (2H, m. CH_2), 2.89 (2H, t, J=7.5Hz. CH_2), 3.65 (1H, br s, OH), 3.74 (2H, t, J=7.5Hz. CH_2), 7.14 (1H, d. J=2.3Hz. Ar-H), 7.44-7.52 (2H, m. Ar-H), 7.85 (1H, s. Ar-H), 7.92 (1H, s, Ar-H), 8.00 (1H. s. Ar-H). 8.43 (1H. br s. NH).

2. (±)-1-[3-(5-(1,2,3-Triazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine. Dihydrogen Maleate

The title-*compound* was prepared from the preceding homotryptophol and (±)-4-[2-(4-fluorophenyl)propyl]piperazine using the procedures described for Example 10. The dihydrogen maleate salt was prepared, mp 177-178°C, (Found: C, 60.19; H, 5.71; N, 12.21. $C_{26}H_{31}N_6F$. $2.0(C_4H_4O_4)$ requires C, 60.17; H, 5.79; N, 12.38%), m/e 447 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.17 (3H, d, J=6.9Hz, Me), 1.94-2.06 (2H, m, CH_2), 2.50-3.56 (15H, m, CH and 7 of CH_2), 6.14 (maleate-H's), 7.08-7.13 (2H, m, Ar-H), 7.26-7.30 (2H, m, Ar-H), 7.34 (1H, d, J=2.0Hz, Ar-H), 7.52-7.57 (2H, m, Ar-H), 7.94 (1H, s, Ar-H), 8.00 (1H, s, Ar-H), 8.70 (1H, s, Ar-H), 11.18 (1H, s, NH).

EXAMPLE 13

1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(3-fluorophenyl)-3,3,3-trifluoropropyl]piperazine. Sequioxalate. Hemihydrate

1. 3,3,3-Trifluoro-2-(3-fluorophenyl)propionaldehyde

The title-*compound* was prepared as described in EP 0240978, δ (250MHz, $CDCl_3$) 4.22-4.33 (1H, m, CH), 7.04-7.48 (4H, m, Ar-H), 9.76-9.80 (1H, m, C*HO*).

2. 1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(3-fluorophenyl)-3,3,3-trifluoropropyl]piperazine. Sequioxalate. Hemihydrate

The title-*compound* was prepared as described for Example 8, step 2. The sesquioxalate hemihydrate salt was prepared, mp 105°C (dec.), (Found: C, 53.73; H, 5.14; N, 13.16. $C_{26}H_{28}N_6F_4$. $1.5(C_2H_2O_4)$. $0.5H_2O$ requires C, 54.04; H, 5.00; N, 13.04%), m/e 501 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.92-2.04 (2H, m, CH_2), 2.42-4.20 (15H, m, CH and 7 of CH_2), 7.14-

7.50 (7H, m, Ar-H), 7.77 (1H, s, Ar-H), 9.00 (2H, s, Ar-H), 11.15 (1H, s, NH).

EXAMPLE 14

1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(2,2-difluoro-2-phenylethyl)piperazine. Hydrogen Oxalate

1. 2,2-Difluoro-2-phenylacetic acid

a) Ethyl benzoylformate (1.13g, 0.0063mol) was dissolved in anhydrous CH_2Cl_2 (30ml) and diethylaminosulfurtrifluoride (DAST, 1.0ml, 0.0086mol) added. The reaction mixture was heated to 40°C and left stirring for 4h. The reaction was cooled, poured into a mixture of $NaHCO_3$/ice-water and the product extracted into ether (50ml). The organic layer was dried over $MgSO_4$, evaporated and the residue chromatographed on silica eluting with 2% ether/petrol to yield 0.96g (76%) of 2,2-difluoro-2-phenylacetic acid ethyl ester as a colourless oil. δ (250MHz, $CDCl_3$) 1.26 (3H, t), 4.29 (2H, q), 7.50 (3H, m), 7.62 (2H, m).

b) The ethyl ester from above was dissolved in H_2O/THF (1:1, 20ml) and cooled to 0°C. Sodium hydroxide (1g) was added and the reaction stirred for 1h. TLC (5% ether/hexane) showed complete disappearance of the starting ester. The reaction was acidified to pH 2 with 10% HCl and the product extracted into ether. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to yield the title compound as a solid (1.0g).

2. 1-(*tert*-Butoxycarbonyl)-4-(2,2-difluoro-2-phenylacetamido)-piperazine

2,2-Difluoro-2-phenylacetic acid (0.600g, 0.0035mol), *N*-(*tert*-butoxycarbonyl)piperazine (0.714g, 0.0038mol) and triethylamine (0.53ml, 0.0038mol) were added sequentially to 20ml anhydrous dichloromethane under N_2 at 25°C. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.967g, 0.0038mol) was added and the reaction stirred for 2h. The reaction mixture was diluted with ethyl acetate (50ml) and washed with H_2O (20ml), brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica eluting with 20-40% ethyl acetate-hexane to yield the title compound as a colourless oil (1.0g, 84%). δ (250MHz, $CDCl_3$) 1.44 (9H, s), 3.21 (2H, m), 3.24 (4H, m), 3.44 (2H, m), 7.45-7.62 (5H, m).

3. *N*-(2,2-Difluoro-2-phenylethyl)piperazine

1-(*tert*-Butoxycarbonyl)-4-(2,2-difluoro-2-phenylacetamido)piperazine (1.0g, 0.0029mol) was dissolved in anhydrous THF (10ml) and borane-tetrahydrofuran complex (1.0M in THF, 4.4ml, 0.0044mol) added at 25°C, under N_2. The reaction mixture was heated to reflux for 4h, cooled, and quenched with MeOH (2ml). The volatile solvents were removed *in vacuo* and the residue dissolved in acetone (15ml). The flask was cooled to 0°C and treated with 15ml of 4N HCl. The reaction was stirred at 25°C for 30min and basified with 4N NaOH. The compound was extracted into EtOAc (3x50ml), the organic layer dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was chromatographed on alumina (Grade III), eluting with 1-5% $MeOH/CH_2Cl_2$, then NH_3:MeOH:CH_2Cl_2 (1:5:95) to yield the amine as an oil (0.530g). δ (250MHz, $CDCl_3$) 2.52 (4H, m), 2.79 (4H, m), 2.93 (3H, t, J=5Hz), 7.41 (3H, m), 7.49 (2H, m).

4. 1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(2,2-difluoro-2-phenylethyl)piperazine. Hydrogen Oxalate

Prepared according to Example 1. The hydrogen oxalate salt was prepared, mp 175-177°C, m/e 451 $(M+1)^+$, δ (250MHz, $CDCl_3$), 1.90 (4H, m), 2.43 (4H, m), 2.60 (4H, m), 2.77 (2H, t, J=3Hz), 2.94 (2H, t, J=8Hz), 7.12 (2H, m), 7.39-7.45 (5H, m), 7.51 (2H, m), 8.42 (1H, br s, NH), 8.46 (2H, s, Ar-H).

EXAMPLE 15

(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(2-phenylpropyl)piperazine. 2.1 Hydrogen Maleate. 0.5 Hydrate

To a solution of Intermediate 3 (0.250 g, 0.8 mmol) in MeOH (35 ml) was added 2-phenylpropionaldehyde (0.134 g, 1.0 mmol), glacial acetic acid (0.119 ml, 2.15 mmol) and sodium cyanoborohydride (0.063 g, 1.0 mmol) and the mixture stirred at room temperature for 2h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (2x) and saturated K_2CO_3 solution. The organic layer was dried ($MgSO_4$) and evaporated under vacuum, and the residue chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (90:5:0.5) to give the title *phenethyl piperazine* (0.10 g, 29%). The 2.1 hydrogen maleate 0.5 hydrate salt was prepared, mp. 166-167°C, (Found: C, 60.94; H, 6.06: N, 12.04. $C_{26}H_{32}N_6$. 2.1($C_4H_4O_4$) 0.5 H_2O requires C, 60.64: H, 6.12; N, 12.33%), m/e 429 $(M+1)^+$, δ (250MHz, on free base, $CDCl_3$) 1.24 (3H, d. J=6.90Hz, CH_3), 1.90 (2H, m. CH_2), 2.39-2.47 (12H, m, 6 of CH_2), 2.74-2.80 (2H, m. CH_2), 2.86-3.00 (1H. m, CH), 6.98-7.31 (7H, m. Ar-H), 7.50 (1H. d, J=8.54Hz. Ar-H), 7.55 (1H. d, J=2.03Hz, Ar-H), 8.47 (2H, s. Ar-H), 9.30 (1H. s. NH).

EXAMPLE 16

(±)-1-[3-(5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(3-fluorophenyl)-3-hydroxypropyl]piperazine. 2.625 Hydrogen Oxalate. 1.5 Diethyl etherate

The title compound was prepared from methyl 2-(3-fluorophenyl)propenoate using the procedures described for Example 3, (Found: C, 55.32; H, 6.76; N, 9.99. $C_{26}H_{31}N_6FO$. 2.625($C_2H_2O_4$). 1.5$(C_2H_5)_2O$ requires C, 55.22; H, 6.37; N, 10.37%), m/e 463 $(M+1)^+$.

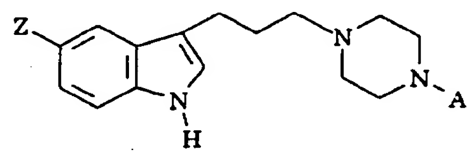
EXAMPLE 17

(±)-1-[3-(5-(2-Methylimidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine. 3.25 Hydrogen Maleate

The title-compound was prepared from 4-(2-methylimidazol-1-yl)phenylhydrazine using the procedures described for Example 8 part 1 and Example 5 part b, (Found: C, 58.65; H, 5.92; N, 8.71. $C_{28}H_{34}N_5F$. 3.25($C_4H_4O_4$) requires C, 58.85; H, 5.66; N, 8.37%).

CLAIMS:

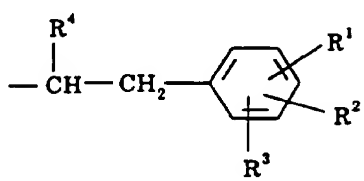
1. A compound of formula I, or a salt or prodrug thereof:



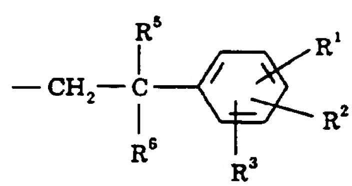
(I)

wherein

A represents a group of formula (i) or (ii):



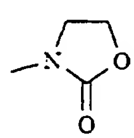
(i)



(ii)

in which

R^1 represents hydrogen, halogen, trifluoromethyl, C_{1-6} alkoxy or a group of formula (a):


;

(a)

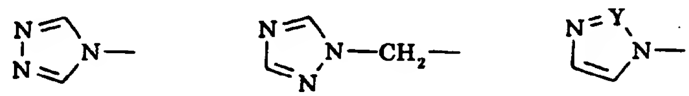
R^2 and R^3 independently represent hydrogen, halogen, trifluoromethyl or C_{1-6} alkoxy;

R^4 represents C_{1-6} alkyl, hydroxy(C_{1-6})alkyl or C_{1-6} alkoxy(C_{1-6})alkyl;

R^5 represents halogen, trifluoromethyl, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl or C_{1-6} alkoxy(C_{1-6})alkyl; and

R^6 represents hydrogen or halogen;

Z represents a group of formula (Za), (Zb) or (Zc):



(Za) (Zb) (Zc)

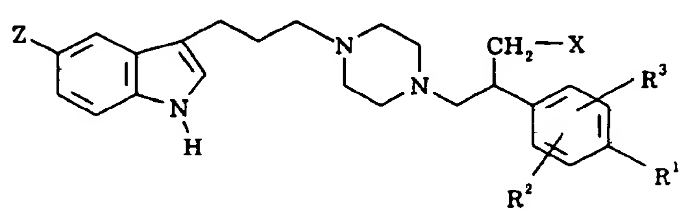
in which

Y represents nitrogen or C-R^7; and

R^7 represents hydrogen or C_{1-6} alkyl.

2. A compound as claimed in claim 1 wherein A represents a group of formula (i) or (ii) in which R^5 represents C_{1-6} alkyl, hydroxy(C_{1-6})alkyl or C_{1-6} alkoxy(C_{1-6})alkyl, and R^6 represents hydrogen; and Z represents a group of formula (Za) as defined in claim 1.

3. A compound as claimed in claim 1 represented by formula II, and salts and prodrugs thereof:



(II)

wherein Z. R^1, R^2 and R^3 are as defined in claim 1; and

X represents hydrogen, hydroxy or methoxy.

4. A compound selected from:

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(3-hydroxy-2-phenylpropyl)piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(3-methoxy-2-phenylpropyl)piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)-3-hydroxypropyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)prop-2-yl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-hydroxyprop-2-yl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[1-(4-fluorophenyl)-3-methoxyprop-2-yl]piperazine;

and salts and prodrugs thereof.

5. A compound selected from:

1-[3-(5-(imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-(2-phenylpropyl)piperazine;

1-[3-(5-(imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine;

1-[3-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(3-fluorophenyl)-3-methoxypropyl]piperazine;

1-[3-(5-(1,2,3-triazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(3-fluorophenyl)-3,3,3-trifluoropropyl]piperazine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(2,2-difluoro-2-phenylethyl)piperazine;

and salts and prodrugs thereof.

6. A compound selected from:
1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(3-fluorophenyl)-3-hydroxypropyl]piperazine;
1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(2-phenylpropyl)-piperazine;
1-[3-(5-(2-methylimidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-fluorophenyl)propyl]piperazine;
and salts and prodrugs thereof.

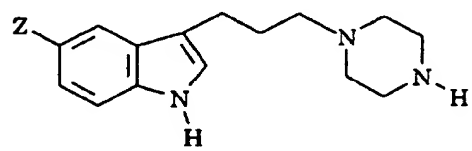
7. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier.

8. A compound as claimed in any one of claims 1 to 6 for use in therapy.

9. The use of a compound as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which an agonist of 5-HT_{1D} receptors selective for the 5-HT_{1D_α} subtype thereof is indicated.

10. A process for the preparation of a compound as claimed in claim 1, which comprises:

(A) reacting a compound of formula III with a compound of formula IV:



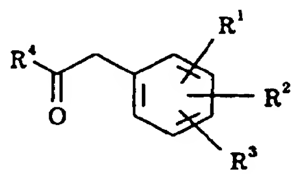
(III)

$$L^1 - A$$

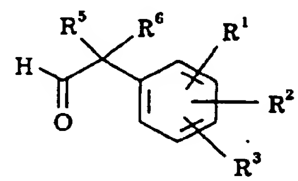
(IV)

wherein A and Z are as defined in claim 1, and L^1 represents a suitable leaving group; or

(B) reacting a compound of formula III as defined above with a compound of formula VA or VB respectively:



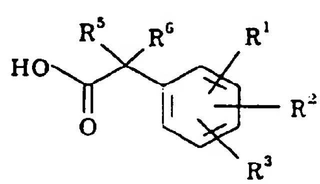
(VA)



(VB)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in claim 1; in the presence of a reducing agent; or

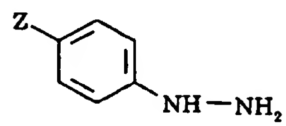
(C) reacting a compound of formula III as defined above with a carboxylic acid derivative of formula VI:



(VI)

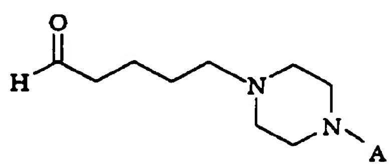
wherein R^1, R^2, R^3, R^5 and R^6 are as defined in claim 1; in the presence of a condensing agent; followed by treatment with a reducing agent; or

(D) reacting a compound of formula VII:



(VII)

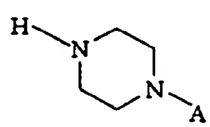
wherein Z is as defined in claim 1; with a compound of formula XII, or a carbonyl-protected form thereof:



(XII)

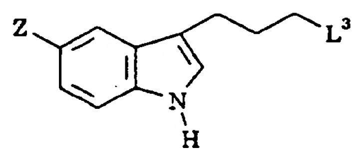
wherein A is as defined in claim 1; or

(E) reacting a compound of formula XIV:



(XIV)

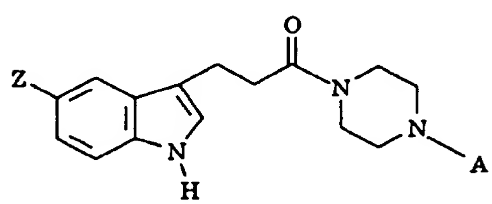
wherein A is as defined in claim 1; with a compound of formula XV:



(XV)

wherein Z is as defined in claim 1, and L^3 represents a suitable leaving group; or

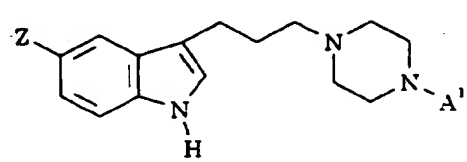
(F) reducing a compound of formula XVIII:



(XVIII)

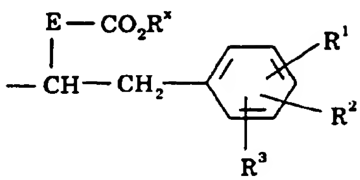
wherein Z and A are as defined in claim 1; or

(G) reducing a compound of formula XX:

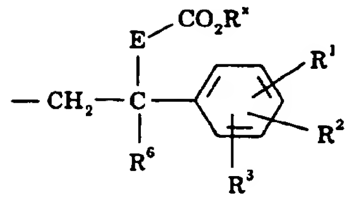


(XX)

wherein Z is as defined in claim 1, and A^1 represents a group of formula (iii) or (iv):



(iii)



(iv)

in which E represents a chemical bond or a C_{1-5} alkylene chain, R^x represents C_{1-6} alkyl, and R^1, R^2, R^3 and R^6 are as defined in claim 1; and

(H) subsequently, if desired, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

11. A method for the treatment and/or prevention of clinical conditions for which an agonist of 5-HT_{1D} receptors selective for the 5-$HT_{1D\alpha}$ subtype is indicated, which method comprises administering to a patient in need of such treatment an effective amount of a compound as claimed in any one of claims 1 to 6.

INTERNATIONAL SEARCH REPORT

Intern   al Application No
PCT/GB 96/02309

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/40 C07D403/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 548 813 A (BRISTOL-MEYERS SQUIBB COMPANY) 30 June 1993 cited in the application see claims	1,7
A	WO 94 02477 A (MERCK SHARP & DOHME LTD.) 3 February 1994 see claims	1,7,9
P,X	WO 95 32196 A (MERCK SHARP & DOHME LTD.) 30 November 1995 see claims	1,7,9
P,X	WO 96 16056 A (MERCK SHARP & DOHME LTD.) 30 May 1996 see claims	1,7,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
29 November 1996	05.12.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 96/02309

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 96/02309

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-548813	30-06-93	AU-B- 661527	27-07-95
		AU-A- 3003492	24-03-94
		CA-A- 2084531	20-06-93
		CZ-A- 9203592	19-01-94
		JP-A- 5262762	12-10-93
		NZ-A- 245439	26-07-95
		US-A- 5434154	18-07-95
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		CN-A- 1085556	20-04-94
WO-A-9402477	03-02-94	AU-B- 672802	17-10-96
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		EP-A- 0651749	10-05-95
		JP-T- 7509452	19-10-95
		US-A- 5567726	22-10-96
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WO-A-9616056	30-05-96	AU-A- 3875095	17-06-96